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REVIEW

ADVANCES IN RADIOCHEMOTHERAPY IN THE TREATMENT OF HEAD AND NECK CANCER

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New advances are being incorporated into the radiochemotherapy treatment of squamous cell carcinoma of the head and neck. Although the overall prognosis is poor in advanced stages, the possibility of incorporating combined protocols of chemotherapy and radiotherapy for organ preservation or for palliation in cases of recurrent/locally advanced stages that are not good surgical candidates must not be forgotten. In this context, there is an urgent need to incorporate quality of life questionnaires and functional evaluation into organ-preservation studies, as well as to assure the importance of surgical salvage after radiotherapy and chemotherapy protocols.

The authors provide an extensive review of the advances occurring in the nonsurgical treatment of head and neck cancer. Special attention is given to different radiotherapy protocols, new chemotherapy combinations, molecular markers, and molecular therapy as well as the possibility of incorporating re-irradiation and adjuvant therapy after surgery.

DESCRIPTORS: **Chemotherapy. Radiotherapy. Head and neck cancer.**

Head and neck cancer (HNC) is a major health problem in Brazil as well as in other countries. In the U.S., the annual incidence is about 50,000 new cases/year, and a total of 500,000 will be diagnosed worldwide. Unfortunately, most of the cases are diagnosed in advanced stages of the disease (60% stages III and IV) and are squamous cell carcinoma. Risk factors for HNC are well established, smoking and alcohol consumption being the most important and studied. Recently, the importance of new risk factors such as the Epstein-Barr virus and human papilloma virus have received more attention, especially regarding nasopharyngeal and laryngeal carcinoma, respectively.

In spite of the high prevalence of this disease, studies including radiotherapy and chemotherapy in HNC have been subject to many technical problems. The difficulty is attributed at least in part to patient-related problems, such as co-morbidities (due in part to smoking and alcohol consumption), advanced stage of the disease at diagnosis, and the necessity of a multidisciplinary approach including surgery, medical oncology, radiotherapy, nutrition, and speech pathology. In the past few years, some progress has been made in trying to address the importance of protocols involving chemotherapy and radiotherapy for irresecable disease and for organ-preservation strategies.

Randomized studies such as those presented by Brizel[1], Wendt[2], and Merlano[3] clearly demonstrate the benefit of combining chemotherapy with radiotherapy versus radiotherapy alone for locally advanced HNC; these studies involved patients with all sites of HNC. Studies from Calais[4,5] and Al-Sarraf[6] confirmed the superiority of combined strategy for specific sites like the oropharynx and nasopharynx, respectively. Although all these studies reported better locoregional control, and some of them reported survival benefits, unfortunately, toxicity was a limiting factor in most of them.

For organ-preservation purposes, the study run by the Veterans Affair Study Group[7] (VA) with more than 300 patients, comparing sequential treatment with 5-fluorouracil/cisplatin followed by radiotherapy (for those who responded to 2 cycles of induction therapy) with standard laryngectomy followed by radiation, showed no ben-

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efit in terms of survival, but the larynx was preserved in 60% of the patients at the 5-year follow-up. These results were confirmed in a phase III study in hypopharynx tumors run by the Eastern Oncology Group (ECOG)[8].

A recent meta-analysis was presented by Pignon[9], analyzing studies with chemotherapy and radiation. This meta-analysis and another by El-Sayed[10] confirmed the benefit in terms of survival for the use of chemotherapy and radiation in a concomitant fashion; the benefit in terms of survival was 8% compared to 4% for the sequential treatment studies (chemotherapy before radiation); adjuvant studies with chemotherapy alone after surgery did not show benefit in these analysis.

Another important study was presented by Forastiere[11] at the American Congress of Clinical Oncology in 2001, comparing radiotherapy alone versus the VA regimen versus concomitant therapy with cisplatin (100 mg/m^2 every 3 weeks) and radiation. This study also demonstrated the superior outcome for the concurrent radiochemotherapy compared to radiation-only treatment (larynx preserved at 5 years, 85% vs. 64%, and 2-year laryngectomy free-survival 68% vs. 53%).

Our results with concomitant therapy using the same regimen for oropharyngeal and laryngeal tumors were recently presented (Proceedings of ASCO meeting 2003, in press) and confirmed 40% complete responses, although 40% of the patients were not able to complete the 3 cycles of planned chemotherapy.

New directions in the treatment of HNC can be summarized in the following topics:

1. advances in radiation treatment
2. new combinations
3. target / molecular therapy and new molecular markers
4. re-irradiation and concurrent chemotherapy
5. use of new radiology techniques

1. ADVANCES IN RADIATION TREATMENT

Changes in fractionation scheme

Some of the critics who rely on the randomized studies in HNC combining chemotherapy and radiation are concerned with the possibility of technical differences including total dose and fractionation between the studies.

The standard therapy for gross disease is 70 Gy over 7 weeks of therapy (1.8 to 2 Gy/fraction). Studies evaluating hyperfractionation (more than 1 fraction a day) have been presented over the last 5 years. These regimens allowed an increase in total dose to about 80 Gy without increase in complications.

An overview reported significantly improved local and regional tumor control, and 3 of 4 studies reported improved survival using hyperfractionation vs. standard treatment[12].

Dr. Calais[4,5] published the results of a phase III randomized study of oropharynx tumors comparing hyperfractionated radiation alone vs. the same regimen with chemotherapy (cisplatin/5-FU), and demonstrated the feasibility of the combination and the benefit of adding chemotherapy to this radiation scheme.

Another strategy with altered fractionation involves delivery of radiation over a short time interval. The rational for this approach is that there is an accelerated tumor re-population by surviving clonogenic cells at the latter phase of the therapy; this is associated with lower tumor control rates when the therapy is lengthened.

Accelerated fractionated radiation improves local control, but also increases acute toxic effects, especially mucositis. Such a regimen was recently shown to improve locoregional control in head and neck cancer compared with standard radiation treatment in a large study done by the RTOG[13].

A recent randomized study was presented comparing accelerated radiation vs. standard radiation plus chemotherapy[14]. This study did not show benefit in terms of survival and locoregional control for the combination in a short follow-up, suggesting that the intensified radiation could be a new standard; the question of what would be the result for the combination of accelerated radiation and chemotherapy remains open.

Radiation induced toxicity

Some attempts are ongoing to develop strategies that minimize radiation toxicities.

Amifostine is actually the only radioprotective agent available and has been studied in phase II and also a phase III study conducted by Dr. Brizel[15]. There is still a conflict regarding the utility of this drug in reducing xerostomia, mucositis, and dermatitis caused by radiation. Dr. Brizel showed in his study a significant statistical benefit in terms of xerostomia and a small nonsignificant benefit in terms of mucositis, without evidence of protecting the tumor; additionally, the time required to develop serious mucositis and xerostomia was longer. Although some in vitro studies have suggested that amifostine could also protect the tumor from the effect of radiation, neither the phase II nor the phase III studies showed a detrimental effect of amifostine in terms of response or survival. Based on these results, amifostine should be reserved for situations where the risk of toxicity and the area of radiation is very high (parotid or salivary glands); for that use, the authors recommend subcutaneous administration before each radiation dose.

Another strategy that has recently been studied is intensity-modulated radiotherapy, which allows a computerized optimization of the intensity of multiple beams. This method enables

the desired radiation dose to encompass the targets, while avoiding the major salivary glands and other structures at risk. Results from previous studies confirmed that 70% of parotid gland salivary flow could be preserved, and with potential for improved irradiation of the tumor targets, this strategy has been studied more frequently for nasopharyngeal tumors[16].

2. NEW COMBINATIONS

With the advent of new chemotherapy drugs, novel combinations have been tested in HNC. Some of the most promising agents are paclitaxel, docetaxel, ifosfamide, gemcitabine, and Navelbine.

Gemcitabine is approved for advanced NSCLC and pancreatic cancer. When used alone or even with cisplatin, it showed only moderate activity in metastatic SCCHN. The interest in this agent was higher because of its potential as a radiosensitizer.

Our group tested gemcitabine in a phase I study in very low doses with cisplatin and radiation for 7 weeks in stage IV SCCHN. After evaluating 12 patients, we confirmed previous studies that showed a high degree of activity but with a prohibitive toxicity[17,18].

Paclitaxel is another promising agent and was tested in large phase II and III studies. In a phase III study comparing paclitaxel/cisplatin with cisplatin/5-FU, the results showed no differences in response rates or survival, but the combination with paclitaxel was superior in the quality-of-life analysis. Two studies using the combination of induction therapy with paclitaxel and carboplatin were recently presented[19,20]; these trials from Chicago[19] and Philadelphia[20] used different schedules of the combination, but both showed a high degree of clinical and pathological responses, including complete responses. Of note, organ preservation was a frequently achieved outcome.

Docetaxel has been tested in different combinations, with radiation, or as an induction therapy before surgery[21,22,23]. One of the most active regimens combines docetaxel with cisplatin (with or without 5-FU)[23]. Despite the potential hematological toxicity of this regimen, phase II studies report more than 90% responses and 40% to 60% complete response as induction therapy. A phase III randomized study comparing docetaxel and cisplatin vs. cisplatin and 5-FU for recurrent or metastatic SCCHN is now on its final accrual, and results will be available soon.

It is important to mention that although the sequential regimens did not show survival benefit, it is not yet known whether these new regimens that appear to have higher response rates in phase II trials will demonstrate a different outcome. Most of those studies present not only with an induction treatment, but an induction followed by concurrent chemotherapy and radiation (usually weekly chemotherapy only as a radiosensitizer). These trials offered intensive systemic therapy, aggressive locoregional treatment, and focused surgery. It will be difficult to choose from several new chemotherapy regimens—cisplatin/5-FU, paclitaxel/carbo bolus, or weekly docetaxel/cisplatin with or without 5-FU—which is the best as induction or concomitant therapy. Only large phase III trials will be able to build on the foundation of the current phase II trials. These trials will also have to assess toxicity, quality of life, costs, and especially the survival benefit of the regimen.

Our experience confirmed the difficulty of administering combined therapy with cisplatin 100 mg/m^2 and radiation to patients with locally advanced larynx and oropharynx cancer, even with the selection of performance status 0 and 1 patients; the toxicity is very high, and results are worst with more advanced disease (stage IVb)[24]. This combination should be considered the standard treatment for organ preservation protocols until the completion of the ongoing phase III studies. We recommend that this therapy only be given in institutions with experience in treating this disease and with a complete multi-disciplinary team.

3. TARGET / MOLECULAR THERAPY AND NEW MOLECULAR MARKERS

The last 20 years of basic research in the mechanisms of cancer development and progression have revealed a number of potential therapeutic targets[25]. This work has culminated in the generation of a number of novel molecular targeted agents. These agents are important not only for increasing clinical responses, but primarily for providing better prognostic indicators of patient survival or even for selecting the best treatment based on the molecular analysis of the tumor.

EGFR

The single most important molecular target for SCCHN has been the epidermal growth factor receptor (EGFR), which is overexpressed in 40% to 90% of the patients[26]. Epidermal growth factor receptor is a member of the ERBb family of tyrosine-kinase (tk) receptors found on the cell surface. It is overexpressed on the majority of SCCHN, and it appears to be an early event in carcinogenesis. Activation of EGFR is related to cell proliferation, protection from apoptosis, and production of proinflammatory cytokines.

Two principal methods for inhibiting EGFR have been identified and studied in clinical trials: antibodies to EGFR and small molecules that inhibit the enzymatic function of the receptor

by binding to intracellular tyrosine kinase.

Cetuximab (c225) is the most studied antibody and has engendered a lot of controversy. Single agent activity of the antibody is marginal; however, a lot of interest came from combination with cisplatin and especially with radiation. Three trials of cetuximab and cisplatin were presented at the 2002 American Oncology Meeting (ASCO)[27,28,29]; activity was suggested with this combination in patients considered refractory to previous cisplatin chemotherapy. A trial presented by Dr. Baselga had a 14% response rate after progression on platin-based regimens. The Eastern Cooperative Oncology Group is now completing a phase III trial with cisplatin and cetuximab or placebo; yearly results suggest higher response rates without disease-free survival difference.

Robert et al.[30] presented in a phase I trial the interaction of cetuximab with radiation and showed that this combination was very effective (100% response rate) as a radiosensitizer without excessive toxicity, which was already suggested by in vivo studies. A randomized trial has recently ended accrual.

Two small molecules known as gefitinib (ZD 1839) and OZI-774 also have been evaluated in SCCHN. A phase I study showed some activity, and a phase II study was presented in the 2002 ASCO meeting[31]. A total of 52 patients with recurrent or metastatic SCCHN (mostly treated with chemotherapy) were treated with ZD 1839 500 mg orally, and there was a surprisingly 20% response in 40 available patients.

In a large phase II study presented by Senzer[32] with 124 patients, the response rate to OZI-774 was 5.6% (partial response) and 39% stable disease; this was not associated with EGFR status. Our group is now starting a phase II trial of OZI-774 concurrent with cisplatin 100 mg/m^2 weekly for 3 weeks and radiation (70 Gy) for locally advanced SCCHN.

Reasons for the enthusiasm in testing these compounds are related to the possibility of oral use (OZI-774 and ZD 1839) and the lower incidence of toxicity, mostly skin rash and mild diarrhea, as well as the molecular mechanism of action that allows future combination with chemotherapy.

Gene therapy

Virus-based therapy for HNC has been evolving for some time. Results have been published with onyx-015, adp53, and others[33,34]. Unfortunately, it is still not known how to best use these therapies, which are still reserved for a small group of patients who can receive therapy as an intratumoral injection. A study of gene therapy in combination with radiation and another phase III study comparing gene therapy with chemotherapy for recurrent disease are ongoing.

Molecular/genetic markers

p53. In head and neck cancers, p53 mutations are present in 33% to 59% of tumors as determined by PCR, loss of heterozygosity occurs in 38%, and abnormal immunohistochemical staining occurs in 37% to 76% of tumors[35]. There is a lot of controversy regarding the status of p53 as a marker for prognosis and survival; this could reflect a methodology problem or the small number of patients in some studies. Studies evaluating the adequacy of surgical margins showed that in patients with histologically and genetic negative margins (p53 negative in the margin), the incidence of recurrence is lower than when the p53 is mutated in the margin (genetically positive)[36]. At the moment, p53 mutations should not be considered as a predictor of survival or used to select patients for different treatments

EGFR. Besides the high percentage of overexpression of this marker (40% to 90%) and the potential for target treatments directed to block this receptor, there are only a few studies that suggest that patients with overexpression have worse survival. In a recent study presented by Bensadourn et al.[37] with 92 patients who underwent hyperfractionated radiation and chemotherapy, overexpression of EGFR was a major prognostic factor in univariate and multivariate analysis.

p16/p21/p27. These are tumor suppressor genes that act to modulate cell proliferation. Abnormalities of these genes are frequent in SCCHN and had been related to worse survival, increased recurrences, tumor progression, and nodal metastasis in some studies.

4. RE-IRRADIATION AND CONCURRENT CHEMOTHERAPY

Re-irradiation with concurrent chemotherapy is a new approach that has been increasingly studied in recent years; this is based on the high rate of locoregional recurrences in previously irradiated sites and secondary primary head and neck cancers. The standard of care of previously irradiated nonresectable recurrent head and neck cancer has been chemotherapy alone; however, chemotherapy alone results in limited palliation with no long-term survivors (response rates 10% to 50% and a median survival time of 6 months).

It must be assumed that the majority of tumors that recur after radiation have arisen from selected resistant cells. Therefore, re-irradiation alone, especially with low doses, is not likely to be effective. This approach is considered to be a potentially curative option for recurrent nonresectable disease arising in irradiated areas. Results from several centers reveal varying outcomes, with 5-year survival ranging

from 9% to 93% in selected series[38,42]. The differences could be attributed to variations in patient selection, anatomic sites, radiation dosages, and concurrent chemotherapy.

A recent series from the University of Chicago[39,40] included patients treated with 5-fluorouracil, and hydroxyurea concomitant with twice-daily re-irradiation consisting of 1.5 Gy bid to a total dose of 75 Gy (60 Gy in previous treatment with optimal surgical debulking). Treatment was given in alternating weeks (5 days followed by a 9–day break). With a median follow-up of 48 months, the 3-year survival and locoregional control were 29% and 42% respectively.

The radiation therapy oncology group (RTOG) reported the results of 86 patients treated with alternating weeks of hyperfractionated radiotherapy and concomitant chemotherapy (with 5-FU and hydroxyurea). With a total dose of radiation of 60 Gy and a follow-up of only 16 months, the 1-year and 2-year survival were 42% and 16%, respectively. A new RTOG protocol 99-11 is now accruing patients to a regimen consisting of paclitaxel and cisplatin with split-course hyperfractionated radiotherapy.

There are several prognostic factors that influence the results of the re-irradiation protocols. The first is the possibility of optimal surgical debulking before treatment, as shown by the work of Haraf et al. who reported that optimal debulking was significantly predictive of freedom from progression at any site and freedom from locoregional progression. The second is the anatomic site, since reported outcomes seen in patients with recurrent nasopharynx and laryngeal carcinoma seemed encouraging in selected series. Third is the time interval, since prior irradiation and re-irradiation dose are also strong predictors of outcome. A study from Spencer et al.[41] suggested that time to re-irradation greater than 24 months was predictive of longer median survival (15 months) compared to re-irradiation within 1 year (ms 6.5 months). Arguments for high-dose re-irradiation are based on the probability of the presence of radio-resistant cells that recurred after previous therapy. Most of the studies showed that re-irradiation with doses greater than 58 Gy were related to longer survival[41].

It is important to emphasize that re-irradiation must be undertaken in institutions with experience in dealing with these patients and with a multidisciplinary team, since toxicity to skin, mucous membranes, and blood cells, as well as death related to treatment have been reported in most of the series.

5. USE OF NEW RADIOLOGY TECHNIQUES

One of the recurring problems in dealing with SCCHN is the difficulty in evaluating the response after treatment with chemotherapy and radiation.

The PET scan (positron emission tomography) is being considered a new tool for HNC diagnosis, staging, and also restaging of head and neck cancers[43,44]. In cases of unknown primary tumors of the head and neck, PET is able to identify 20% to 40% of the cases; in tumor staging, the reported sensitivity and specificity are 83% and 93%, respectively. Since local recurrences are very common in this disease, PET has also been used to evaluate residual disease as well as recurrence in the neck. In a study by Lindholm et al.[44], PET was used before and after radiotherapy and was related to complete responses after irradiation.

Radiochemotherapy after surgery

Studies including adjuvant treatment after surgery are, at the moment, not conclusive. Two important studies were recently presented showing a possible advantage of using radiation and chemotherapy in high-risk patients after surgery. The first study by Cooper et al.[45] in 228 patients considered high-risk after surgery (T3-4 or N2-3 or extracapsular disease or positive margins), were randomized between radiotherapy (66 Gy) or radiotherapy plus cisplatin 100 mg/m^2 every 3 weeks. The preliminary analysis demonstrated no improvement in locoregional control or survival, but disease-free survival was better for combined treatment, and toxicity was also very high. In a similar study run by the EORTC[46] with 334 patients, the combined therapy had higher local control, disease-free survival, and overall survival, with no excessive toxicity. The difference in results could be explained by the number of patients, selection of patients, or short follow-up, but definitive conclusions are not possible at this moment. Since both trials showed at least an increase in disease-free survival, radiochemotherapy could be an option for high-risk patients with a younger age and good performance status.

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RESUMO

HERCHENHORN D e col. **-** Avanços no tratamento quimioterápico e radioterápico do Câncer de cabeça e pescoço. **Rev. Hosp. Clín. Fac. Med. S. Paulo 59**(1):39-46, 2004.

Novos avanços vêm sendo incorporados no tratamento radio e quimioterápico do Câncer Epidermóide de Cabeça e Pescoço. Apesar do prognóstico reservado dos tumores avançados, não devemos esquecer da possibilidade de incorporarmos protocolos combinados de quimioterapia e radioterapia com intuito de preservação de órgãos ou paliação em estágios de doença recorrente ou localmente avançada que não são bons candidatos à cirurgia. Nesse contexto, há uma necessidade urgente de incorporar questionários de qualidade de vida e avaliação funcional nos estudos de preservação de órgãos, além de assegurar a importância do resgate cirúrgico depois de protocolos radio-quimioterápicos.

Os autores realizam uma extensa revisão dos avanços que vêm ocorrendo no tratamento não cirúrgico do câncer de cabeça e pescoço, com especial atenção à diferentes protocolos de radioterapia, novas combinações de quimioterapia, terapia e marcadores moleculares bem como a incorporação de terapia de re-irradiação e tratamento adjuvante após cirurgia.

DESCRITORES: **Quimioterapia. Radioterapia. Câncer de cabeça e pescoço.**

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